BMJ open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000132
Article Type:	Research
Date Submitted by the Author:	18-Apr-2011
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Subject Heading:	Epidemiology
Keywords:	EPIDEMIOLOGY, DIABETES & ENDOCRINOLOGY, statins, cardiovascular disease, mortality

Effects of statin medication on mortality risk associated with type 2 diabetes in older persons

The population-based AGES-Reykjavik Study

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Running title: Statins and mortality in T2D

Abstract: 258 words. Main text: 2721 words. Three tables and one figure.

Supplement with two tables and two figures.

ABSTRACT

Objective To examine if the beneficial effect of statin medication on mortality seen in randomised clinical trials of type 2 diabetes, applies equally to observational studies in the general population of older people.

Design A prospective, population-based cohort study.

Setting Reykjavik, Iceland.

Participants 5152 men and women from the Age, Gene/Environment Susceptibility - Reykjavik study, mean age 77 years, range of 66-96 years.

Main outcome measure Cardiovascular and all-cause mortality rates and the relative risk of dying according to statin use and history of coronary heart disease (CHD) in persons with type 2 diabetes and those without diabetes with a median follow up time of 5.3 years, until end of 2009.

Results The prevalence of type 2 diabetes was 12.4% of which 35% used statins. Statin use was associated with a 50% (95% confidence interval 8% to 72%) lower cardiovascular mortality and 53% (29% to 68%) lower all-cause mortality rates in persons with diabetes. For those without diabetes, statin use was associated with a 16% (-24% to 43%) lower cardiovascular and 30% (11% to 46%) lower all-cause mortality rates. Persons with diabetes using statins had a comparable risk of cardiovascular and all-cause mortality as the general population without diabetes. The effect was independent of the level of glycemic control.

Conclusion This observational study lends important support to existing data from randomised clinical trials. Our data suggest that in the general population of older people with diabetes, statin medication markedly reduces the excess cardiovascular and all-cause mortality risk, irrespective of the presence or absence of CHD or glucose-lowering medication.

Article focus

- Clinical trials have shown that statin medication is beneficial for persons with diabetes as regards cardiovascular morbidity and mortality.
- This is not well established except within the rigours of randomised clinical studies.

Key message

- This population-based observational study of older individuals demonstrates that treatment with statins in persons with diabetes reduces cardiovascular mortality rate to a level comparable to what is observed in those without diabetes.
- The effect observed is of comparable magnitude to the effect reported in randomised clinical trials.

Strengths and limitations of this study

- A major strength of the study is the proportionally large national representation in this population-based cohort, the high participation rate and the comprehensive information on morbidity and mortality. The effect observed is of comparable magnitude to the effect reported in randomised clinical trials.
- A limitation is the non-attendance of frail individuals in the study that may cause a possible bias. Non-attendees in the study have been shown, however, at earlier visits to have comparable levels of conventional cardiovascular risk factors. A weakness in our study is the relatively low number of events during the five-year follow-up.

Key words Cohort study, type 2 diabetes, statins, older persons, cardiovascular disease mortality, AGES-Reykjavik

Abbreviations

AGES-Reykjavik, Age, Gene/Environment Susceptibility - Reykjavik Study; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CHD, coronary heart disease; 95% confidence interval, 95%CI; CRP, C-reactive protein; CVD, cardiovascular disease; HbA_{1c}, haemoglobin A_{1c}; ICD-9 and ICD-10, International Statistical Classification of Diseases and Related Health Problems 9^{th} and 10^{th} Revision; MI, myocardial infarction; PCI, percutaneous transluminal coronary intervention; SD, standard deviation; TG, triglycerides; WHO, World Health Organization

INTRODUCTION

The excess risk of vascular disease in persons with diabetes is about twofold compared with those without diabetes and is independent of other conventional cardiovascular risk factors. This was clearly demonstrated in the meta-analysis from 102 prospective trials, recently published by the Emerging Risk Factors Collaboration[1]. The beneficial effects of statins in reducing major vascular events in patients with diabetes, irrespective of their baseline lipid levels, have been demonstrated in a number of randomised clinical trials[2-5]. Additionally, improved life expectancy in recent years of persons with type 2 diabetes, relative to those without diabetes, has been reported[6-8], although a difference still exists. This improvement is possibly a result of better adherence to published clinical guidelines, advocating aggressive multifactorial treatment[9]. However, many patients with type 2 diabetes are still not receiving treatment with statin medication[10, 11]

Although randomised clinical trials have clearly demonstrated the benefit of statin use with regard to cardiovascular morbidity and mortality, every physician will daily face the question whether these trial results apply to his patient. A general population of individuals, with a varied background of co-morbidities which may or may not have excluded them from participation, is not fully represented in the aforementioned trials. This is why it is of key importance to gather confirmatory information from population-based observational studies. One recent prospective population-based study[10] from the U.K. General Practice Database has indeed reported the beneficial effect of statin treatment in lowering all-cause mortality in type 2 diabetes. Older persons are under-represented in clinical trial data and it is therefore particularly important to obtain information on the potential improvement in life expectancy with statin use in older persons with type 2 diabetes, as well as data on the relative impact of lipid lowering treatment in that age group. This will help in clarifying at a population-based level whether current guidelines

should be applied to older persons, who may have had diabetes for an extended period of time.

The present study addresses this information gap by exploring treatment modalities and cardiovascular and total mortality in older individuals with diabetes in the population-based Age, Gene/Environment Susceptibility (AGES)-Reykjavik study.

METHODS

Study population

Between 2002 and 2006 the AGES-Reykjavik study re-examined 5764 unselected survivors of the original cohort who had previously participated in the Reykjavik Study[12]. In the present study 5152 of these survivors are included, with a mean age of 77 years (range 66-96) and a median follow up time of 5.3 years. Informed consent was obtained from all study participants. The Reykjavik Study cohort originally comprised a random sample of 30 795 men and women born in 1907–1935, living in Reykjavik in 1967 that were invited to participate in a long-term prospective cardiovascular survey. A total of 19 381 attended, resulting in 71% recruitment rate [12].

As part of the baseline examination in the AGES-Reykjavik study, a comprehensive questionnaire was administered. In order to eliminate any persons with type 1 diabetes in the study, participants reporting onset of diabetes before the age of 40 were not included; neither were participants not completing their questionnaire or having incomplete data for other study variables included: 66 had missing data about diabetes history on questionnaire; 21 were considered to have diabetes of type 1; 78 had missing data on risk factors (cholesterol, systolic blood pressure, body mass index, triglycerides); 447 had missing HbA1c. Participants were asked to bring all medications and supplements

used in the previous 2 weeks to the clinic. All participants also had a fasting blood specimen drawn and analysed as documented below.

The criteria used for type 2 diabetes diagnosis was either fasting serum glucose of ≥7mmol/l at the visit to the clinic, based on the WHO recommendations from 1999[13], self-reported diabetes in the questionnaire and/or use of diabetes medication.

Blood samples were drawn after overnight fasting. Total cholesterol, HDL cholesterol, triglycerides, high sensitivity CRP, glucose and HbA1c were analysed on a Hitachi 912, using reagents from Roche Diagnostics and following the manufacturer's instructions. LDL was calculated using the Friedewald equation[14].

Blood pressure was measured with a mercury sphygmomanometer with a large cuff, and the mean value of two consecutive blood pressure measurements was used in the analysis. Height and weight were measured and BMI calculated as kg/m^2.

Information on the causes of death was based on data from a complete registry of deaths available from the Icelandic National Roster. All-cause mortality was defined according to ICD 9-10. In this study we calculated an individual's time at risk from the date of participation in the baseline survey until the date of death from cardiovascular disease (ICD-9 and ICD-10: defined as in the SCORE project[15]) or from all causes, or until the end of follow-up in the cohort. The information is collected from National Health System Records by the Icelandic Heart Association.

The study was approved by the National Bioethics Committee in Iceland (VSN 00-063) as well as the Institutional Review Board of the Intramural Research Program of the National Institute on Aging and the Data Protection Authority in Iceland.

Statistical analyses

Baseline characteristics of participants by sex and diabetic status in the AGES-Reykjavik study were compared using either linear or logistic regression with age adjustment. Skewed variables were log-transformed. The Cox proportional hazards regression model was used to estimate mortality rates and hazard ratios for the effect of risk factors and statin use. The time on study was used as the time scale. For hazard ratio estimates, an adjustment was made for age and sex in a simple model, and additionally for the following cardiovascular risk factors: cholesterol, HDL-cholesterol, systolic blood pressure, BMI, triglycerides, CRP, hypertensive medication, and current smoking. A separate term was used in the survival models to represent subgroups, formed by diabetes, history of CHD and statin use. The mortality rate was estimated from the average of the cumulative hazard function after a five-year follow-up and represented as the rate per 1000 person-years. The proportionality assumption for the hazard ratio associated with type 2 diabetes was inspected graphically and by testing the significance of the interaction of type 2 diabetes statuses with the logarithm of the follow-up of time analysed as a time-dependent covariate. Significance testing was two-sided and based on a 5% probability level. We analysed the data using SAS/STAT® software, version 9.2.

RESULTS

The mean age of the 5152 AGES-Reykjavik study participants was 77.0 (±5.8) years, with an age range of 66-96 years. The baseline characteristics in men and women with and without type 2 diabetes according to statin use are shown in Table 1. A higher percentage of individuals with type 2 diabetes were hypertensive than those without diabetes; they also had lower HDL-cholesterol but higher triglycerides and BMI, irrespective of statin use. Statin medication reduced the mean level of total and LDL-cholesterol similarly in those with and without diabetes, or by about 1.2 mmol/l in both men and women. In statin

users CRP was lower by 0.30 mg/l in men and 0.50 mg/l in women without diabetes and 0.80 and 1.05 mg/l respectively in those with diabetes. The prevalence of coronary heart disease estimated from hospital records in persons without diabetes using statins, was 71.1% in men and 34.4% in women compared to 7.9% and 2.2% respectively in those not using statins. In individuals with diabetes the coronary heart disease prevalence was 59.4% in men and 24.2% in women using statins, compared to 14.8% and 8.6% respectively in those not on statins. Over 93% of all statin users were hypertensive compared to 78% of non-statin users.

The prevalence of type 2 diabetes and use of glucose lowering treatment in men and women is shown in Table 2. About 16% of men and 9.5% of women in the cohort had type 2 diabetes and the proportion of persons with diabetes undiagnosed at baseline was 31%. In the group with previously diagnosed type 2 diabetes, 23% of the men and 35% of the women controlled their blood sugar level with diet only. As shown in Table 2, less than 7% of persons with diagnosed diabetes were simultaneously taking 3 or 4 drugs for lowering blood glucose. For participants with a prior diagnosis of diabetes, the average time from diagnosis at baseline assessment was just over 10 years.

Effect of statins on cardiovascular and all-cause mortality

The five-year average cardiovascular disease mortality and all-cause mortality rates for those with and without diabetes are shown in Figure 1. Mortality rate is estimated according to statin use and prevalence of coronary heart disease, adjusted to age 75, sex and the mean levels of cardiovascular risk factors (cholesterol, HDL-cholesterol, systolic blood pressure, BMI, triglycerides, hypertensive medication and current smoking) within each cohort. About 26% of men and 16% of women without diabetes and about 35% in both sexes with diabetes were statin users. Statin medication was administered to 69.2% of

persons with prevalent coronary heart disease and known diabetes compared to 31.6% of those with known diabetes but without coronary heart disease (Supplement Table 1).

For individuals with diabetes and prevalent coronary heart disease, statin use was associated with a significantly lower rate of cardiovascular disease mortality (Figure 1a) compared to those not using statins, or 11.3 vs. 24.6 per 1000 person years. This amounts to 54% (95% confidence interval 14% to 75%) lower mortality rate in statin users. Similarly statin use was associated with an all-cause mortality rate of 27.8 vs. 63.3 per 1000 person years when comparing the same two groups (Figure 1b), amounting to 55% (31% to 71%) lower mortality rate in statin users. In individuals with diabetes but without coronary heart disease, the rate was 48% (1% to 73%) lower for cardiovascular disease mortality and 52% (26% to 69%) lower for all-cause mortality in the group using statins compared to non-statin users. Combining the groups the hazard of cardiovascular disease mortality was 50% lower in statin users compared to non-statin users and all-cause mortality was 53% lower (Supplement Table 2).

Statin use was associated with 16% (-24% to 43%) lower mortality rate in individuals without diabetes as shown in Figure 1, albeit not statistically significant. For all-cause mortality statin users had 30% (11% to 46%) lower mortality rate than in non-statin users.

The effect of statins was not modified by the level of HbA1c, the use of oral hypoglycaemic or hypertensive medication, or whether the diabetes was prevalent or newly diagnosed (Supplement Figures 1 and 2).

The dramatic effect of statin medication use on mortality rate in persons with diabetes is also reflected in the hazard ratios for the relative risk of cardiovascular and all-cause mortality in individuals with diabetes compared to those without as shown in Table 3. In persons with diabetes and prevalent coronary heart disease not on statins, the relative

risk of dying from cardiovascular disease was 3.33 (2.05 to 5.50) when compared to those without diabetes, after adjusting for age, sex and cardiovascular risk factors. The individuals treated with statins, however, had a relative risk of 1.51 (0.83 to 2.75). In persons with diabetes but without coronary heart disease not on statins, the relative risk was 1.40 (1.03 to 1.89) compared to 0.71 (0.31 to 1.62) for those on statins. Adding CRP to the risk factor adjustment showed minimal attenuation of the hazard ratios (Table 3). This implies that the protective effect of statins is not solely attributable to the effect on these cardiovascular risk factors.

DISCUSSION

The major finding in our population-based AGES-Reykjavik study of older individuals with diabetes is the marked improvement in survival associated with statin medication when compared to those not receiving statins, both with respect to cardiovascular and all-cause mortality. This is independent of prevalent coronary heart disease or glucose-lowering treatment, reducing the mortality rate in individuals with diabetes to a level comparable to those without diabetes.

Statin medication in diabetes has increased gradually during the last decade. Data from the U.K. General Practice Research Database showed an increase in statin use from about 5% in 1996 to 63.5% in women and 71.0% in men in 2005[10], which was associated with hazard ratios of mortality of 0.29 in women and 0.34 in men in the first two years following diagnosis of diabetes. Similarly, in Denmark, only 7% of patients receiving glucose-lowering medication also received statins in 1997, but this had increased to 62% in 2007[11]; information on mortality in that study is however lacking. In our cohort of older persons with diabetes the prevalence of statin medication use was 35% overall. In those with known diabetes but without coronary heart disease the prevalence of statin medication

use was 31.6%, but 11.6% in the newly diagnosed without coronary heart disease. One may speculate if this low prevalence of statin use is due to Icelandic physicians' unawareness of results from recent clinical trials or simply their belief that the evidence does not apply to older patients in general.

It is of course well recognised that statin treatment favourably impacts vascular event rates in both those with and without diabetes. In the Heart Protection Study[2] for example it was concluded that 40 mg of simvastatin daily would probably reduce the rate of first major vascular event by about a third. Similarly a two-year treatment period with atorvastatin in type 2 diabetes in the CARDS study reduced the death rate by 27%, prompting an early termination of the trial[16]. The authors concluded that lipid-lowering treatment should at least receive the same attention as glycemic and blood pressure control in type 2 diabetes patients without a history of cardiovascular disease, which is in harmony with current clinical guidelines. Aggressive multifactorial treatment of high-risk individuals with type 2 diabetes has been shown to be important[9], and may also be appropriate for persons diagnosed above the age of 70. Recent results from several large studies[17, 18] have, however, indicated that caution may be needed as regards aggressive glucose lowering treatment in those with long-established coronary heart disease and diabetes of long duration. In our study, statin use at baseline, but not use of glucose-lowering medication, is associated with the marked reduction of cardiovascular and total mortality rate, reducing mortality in those with diabetes to a level similar to those without diabetes.

Statin medication under the rigors of controlled study conditions in selected individuals has thus been shown to be helpful[2, 4 5]. The novelty of our study is that statin medication also is very likely to be important in older persons in the community, persons

which may or may not fit the stringent criteria of normality imposed for inclusion into randomised clinical trials.

Recently a large meta-analysis[1] demonstrated that the increased cardiovascular mortality seen in type 2 diabetes is not explained by conventional cardiovascular risk factors. This suggests that the effect of the statins on cardiovascular mortality seen in our population-based cohort may reach beyond the statins' effect on cholesterol levels, possibly by reducing the damaging effect of inflammatory agents[19, 20]. Inflammation as measured by CRP, however, does not appear to be the explanation in our study, as adjusting for CRP in the risk models did not attenuate the relative risk although those on statins had markedly lower CRP. This warrants further study.

The prevalence of diabetes in Iceland is changing in the same fashion as in other western societies[21]. Furthermore, the Icelandic population is similar to other western populations with respect to cardiovascular morbidity and mortality[22], and our results are therefore applicable to other Caucasian populations. Thus, considerable additional benefit can be expected by adhering to the current guidelines on statin use in treating individuals with diabetes, also in the older age-groups.

In summary, we have estimated the risk of death from cardiovascular disease and from all causes in a population-based cohort of older persons with type 2 diabetes. The main finding is that statin use, irrespective of glucose-lowering and antihypertensive medication, eliminates the difference in the mortality rate of older persons with type 2 diabetes, compared to those without diabetes. Our study suggests that treatment with statins is paramount in the multifaceted management of type 2 diabetes. Strict adherence to the current guidelines is therefore of key importance for older persons with diabetes, regardless of the presence or absence of cardiovascular disease or the level of glucose or blood pressure control.

Our results urgently call for other population-based studies with comparable information to confirm the effect of statin use on mortality in individuals with type 2 diabetes.

Acknowledgements

This study has been funded by NIH contract N01-AG-1-2100, the NIA Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and Althingi (the Icelandic Parliament). The study is approved by the Icelandic National Bioethics Committee, VSN: 00-063. The researchers are indebted to the participants for their willingness to participate in the study.

Author Contributions: Dr Gudnason had access to all the data and takes full responsibility for the content of this paper. Drafting of the manuscript: Olafsdottir, Aspelund, Benediktsson and Gudnason. Statistical analysis: Olafsdottir and Aspelund. Data collection and preparation: Olafsdottir, Aspelund, Gudnason, Thorsson, Eiriksdottir, Sigurdsson, Launer and Harris. All authors contributed to the interpretation of the results, read and commented on the manuscript and approved the final version.

Conflict of interest statement

Dr Gudnason has funding from National Institutes of Health, Icelandic Heart Association, Icelandic Research Council and the European Union. No conflicts of interest were declared by any other authors.

Funding source's role

The Study's sponsors played no role in the study design, the collection, analysis, and interpretation of data or writing of the report. Dr Gudnason had full access to all the data and had final responsibility for submitting the report for publication.

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Table 1. Baseline characteristics according to statin use in men and women without and with type 2 diabetes (T2D). The AGES-Reykjavik study from 2002-2006.

	Men				Women			
Variables	Statins no		Statins yes		Statins no		Statins yes	
(mean ± SD, IQR or %)	without T2D	with T2D	without T2D	with T2D	without T2D	with T2D	without T2D	with T2D
(number)	(1357)	(230)	(477)	(128)	(2237)	(186)	(442)	(95)
Age in years	77.4 (±5.8)	77.9 (±6.1)	76.0 (±4.8)	75.5 (±4.4)	77.0 (±6.1)	78.7 (±6.0) ***	76.1 (±4.8)	76.3 (±4.5)
Cholesterol mmol/l	5.57 (±0.93)	5.38 (±0.98) **	4.32 (±0.82)	4.14 (±0.84) *	6.19 (±1.05)	5.97 (±1.01) **	4.96 (±0.83)	4.67 (±0.94) **
HDL cholesterol mmol/l	1.46 (±0.40)	1.26 (±0.34) ***	1.40 (±0.37)	1.26 (±0.33) ***	1.75 (±0.45)	1.53 (±0.41) ***	1.70 (±0.40)	1.48 (±0.41) ***
LDL cholesterol mmol/l	3.61 (±0.85)	3.40 (±0.89) **	2.38 (±0.67)	2.21 (±0.68) **	3.90 (±0.98)	3.73 (±0.91) *	2.71 (±0.72)	2.41 (±0.70) ***
TG mmol/l, median (IQR)	0.97 (0.56)	1.33 (0.83) ***	1.01 (0.65)	1.29 (0.98) ***	1.04 (0.63)	1.38 (0.85) ***	1.11 (0.67)	1.57 (0.85) ***
CRP mg/l, median (IQR)	1.90 (2.70)	2.20 (3.53) **	1.60 (2.20)	1.40 (2.10)	2.00 (3.20)	3.15 (5.65) ***	1.50 (2.10)	2.10 (3.30) *
BMI kg/m^2	26.4 (±3.7)	28.3 (±4.2) ***	27.0 (±3.7)	28.4 (±3.7) ***	27.0 (±4.9)	29.0 (±5.5) ***	26.8 (±4.0)	30.2 (±5.1) ***
Systolic BP mm Hg	142.9 (±20.6)	141.1 (±20.7)	144.1 (±20.3)	148.2 (±19.6) ***	142.2 (±21.0)	143.3 3 (±21.8)	143.3 (±20.2)	143.6 (±19.7)
Diastolic BP mm Hg	77.0 (±9.4)	74.7 (±10.8) **	74.4 (±9.7)	74.6 (±10.3)	72.6 (9.3)	70.5 (±10.5)*	71.6 (±10.2)	69.7 (±8.9)
Hypertension %[†]	73.5	88.7 ***	91.6	95.3	78.9	88.7 **	92.5	95.8
Hypertensive medication %	50.0	75.2 ***	85.5	87.5	58.7	79.6***	84.6	90.5
Glucose lowering medication	-	46.1	-	64.1	-	36.6	-	64.2
CHD prevalence %[‡]	7.9	14.8**	71.1	59.4*	2.2	8.6***	34.4	24.2*
Family history MI %	30.1	39.1 **	45.2	41.4	40.2	51.6 **	56.7	53.7
Sports current %	51.0	43.9	54.3	45.3	47.1	40.9	50.7	36.8*
Smoking %	11.9	12.2	9.0	9.4	12.4	10.2	12.9	9.5
Haemoglobin A1c %	5.54 (±0.33)	6.38 (±0.88) ***	5.58 (±0.32)	6.55 (±0.79) ***	5.61 (±0.33)	6.32 (±0.95) ***	5.64 (±0.34)	6.58 (±0.88) ***
Glucose mmol/l	5.57 (±0.50)	7.95 (±2.09) ***	5.58 (±0.53)	7.92 (±2.19) ***	5.44 (±0.51)	7.60 (±2.00) ***	5.41 (±0.52)	7.97 (±2.38) ***

Significance estimates for age-adjusted comparison between those with and without T2D and not using statins (no) and statin users (yes): *p<.05; **p<.01; *** p<.001.
[†]Hypertensive are those with systolic BP>140 mmHg, diastolic BP>90 mmHG or on hypertensive medication.
[‡]Prevalence from history of MI, PCI, and CABG in hospital records.

Table 2. Prevalence of type 2 diabetes (T2D) and glucose lowering treatment in the AGES-Reykjavik study 2002-2006.

AGES-Reykjavik study	Men	Women	Men and women	% of total T2D
Total T2D at baseline % (n)	16.3 (358)	9.5 (281)	12.4 (639)	100
Diagnosed at study entry % (n)	5.1 (113)	2.8 (84)	3.8 (197)	31
With prevalent T2D at study entry % (n)	11.2 (245)	6.7 (197)	8.6 (442)	69
Mean T2D duration in years (±SD)			10.7 (±10.0)	
Glucose lowering treatment in prevalent T2D				
on special diet only % (n)	23.3 (57)	34.5 (68)		
on diabetic medication % (n)	76.7 (188)	65.5 (129)		
thereof using 1 drug % (n)	*43.7 (107)*	*40.1 (79)*		
" using 2 drugs % (n)	*25.7 (63)*	*19.8 (39)*		
" using 3 drugs % (n)	*6.9 (17)*	*4.6 (9)*		
" using 4 drugs % (n)	*0.4 (1)*	*1.0 (2)*		

Table 3. Hazard ratios (HR) for the relative risk of cardiovascular disease (CVD) mortality and all cause mortality in people with type 2 diabetes (T2D) compared to all non-diabetics according to prevalent coronary heart disease (chd) and statin use*. The AGES-Reykjavik study from 2002-2006.

	Adjusted for age and sex		Adjusted for age, sex, and †CVD risk factors		Adjusted for age, sex, †CVD risk factors and CRP	
	HR	95% CI	HR	95% CI	HR	95% CI
Death from CVD						
All T2D	1.71	(1.35 to 2.17)	1.48	(1.15 to 1.90)	1.45	(1.13 to 1.86)
According to chd and statin use:						
T2D with chd not on statins	4.71	(2.93 to 7.58)	3.33	(2.02 to 5.50)	3.20	(1.94 to 5.29)
T2D with chd on statins	1.92	(1.08 to 3.43)	1.51	(0.83 to 2.75)	1.55	(0.85 to 2.82)
T2D without chd and not on statins	1.53	(1.14 to 2.05)	1.40	(1.03 to 1.89)	1.34	(0.99 to 1.82)
T2D without chd and on statins	0.83	(0.37 to 1.85)	0.71	(0.31 to 1.62)	0.75	(0.33 to 1.69)
Death from all causes						
All T2D	1.44	(1.22 to 1.69)	1.35	(1.14 to 1.61)	1.32	(1.11 to 1.57)
According to chd and statin use:						
T2D with chd not on statins	3.48	(2.43 to 4.99)	2.88	(1.98 to 4.18)	2.72	(1.87 to 3.95)
T2D with chd on statins	1.61	(1.10 to 2.37)	1.34	(0.90 to 1.99)	1.37	(0.92 to 2.04)
T2D without chd not on statins	1.34	(1.09 to 1.64)	1.34	(1.08 to 1.64)	1.27	(1.03 to 1.57)
T2D without chd on statins	0.77	(0.46 to 1.28)	0.70	(0.42 to 1.17)	0.73	(0.44 to 1.23)

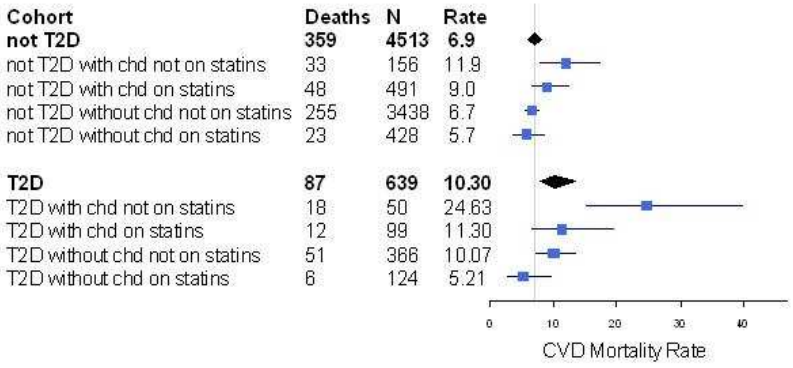
*Individuals on statin medication are identified as on statins, those not on statin medication as not on statins.

†CVD risk factors: cholesterol, HDL-cholesterol, systolic blood pressure, BMI, triglycerides, hypertensive medication, and current smoking.

Figure 1. a) Cardiovascular disease (CVD) mortality rate and b) all cause mortality rate per 1000 person years for subjects without type 2 diabetes (not T2D) and with type 2 diabetes (T2D) according to statin use and prevalent coronary heart disease (chd). Rates have been adjusted to age 75, sex and the mean levels of cardiovascular risk factors (cholesterol, HDL-cholesterol, systolic blood pressure, BMI, triglycerides, hypertensive medication and current smoking) within each cohort. Follow up was through 2009 (a median period of 5.3 years) for the AGES-Reykjavik study. The vertical lines represent the mortality rate of all without diabetes (not T2D, N=4513)

Figure 1

a)



b)

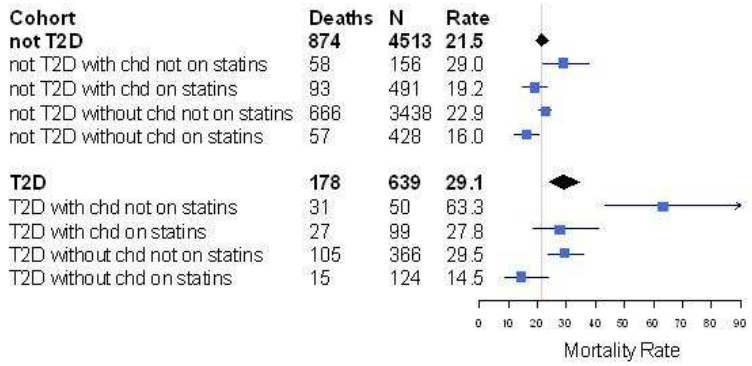


Figure 1. a) Cardiovascular disease (CVD) mortality rate and b) all cause mortality rate per 1000 person years for subjects without type 2 diabetes (not T2D) and with type 2 diabetes (T2D) according to statin use and prevalent coronary heart disease (chd). Rates have been adjusted to age 75, sex and the mean levels of cardiovascular risk factors (cholesterol, HDL-cholesterol, systolic blood pressure, BMI, triglycerides, hypertensive medication and current smoking) within each cohort. Follow up was through 2009 (a median period of 5.3 years) for the AGES-Reykjavik study. The vertical lines represent the mortality rate of all without diabetes (not T2D, N=4513)
180x233mm (96 x 96 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	Not done
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	Separate terms for subgroups in statistical models
		(*c*) Explain how missing data were addressed	6

		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	Not done
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	13
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8-10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Figure 1
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	All analyses are by subgroups
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Effects of statin medication on mortality risk associated with type 2 diabetes in older persons The population-based AGES-Reykjavik Study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000132.R1
Article Type:	Research
Date Submitted by the Author:	13-May-2011
Complete List of Authors:	Olafsdottir, Elin; University of Iceland, Center of Public health Sciences Aspelund, Thor; Icelandic Heart Association, Research Institute Sigurdsson, Gunnar; University of Iceland, Medicine Thorsson, Bolli; Icelandic Heart Association, Research Institute Eiriksdottir, Gudny; Icelandic Heart Association, Research Institute Harris, Tamara; National Institute on Aging, Intramural Research Program Launer, Lenore; National Institute on Aging, Intramural Research Program Benediktsson, Rafn; University of Iceland, Medicine Gudnason, Vilmundur; Icelandic Heart Association, Research Institute
Subject Heading:	Epidemiology
Keywords:	EPIDEMIOLOGY, DIABETES & ENDOCRINOLOGY, statins, cardiovascular disease, mortality

Effects of statin medication on mortality risk associated with type 2 diabetes in older persons

The population-based AGES-Reykjavik Study

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Running title: Statins and mortality in T2D

Abstract: 258 words. Main text: 2721 words. Three tables and one figure.

Supplement with two tables and two figures.

ABSTRACT

Objective To examine if the beneficial effect of statin medication on mortality seen in randomised clinical trials of type 2 diabetes, applies equally to observational studies in the general population of older people.

Design A prospective, population-based cohort study.

Setting Reykjavik, Iceland.

Participants 5152 men and women from the Age, Gene/Environment Susceptibility - Reykjavik study, mean age 77 years, range of 66-96 years.

Main outcome measure Cardiovascular and all-cause mortality rates and the relative risk of dying according to statin use and history of coronary heart disease (CHD) in persons with type 2 diabetes and those without diabetes with a median follow up time of 5.3 years, until end of 2009.

Results The prevalence of type 2 diabetes was 12.4% of which 35% used statins. Statin use was associated with a 50% (95% confidence interval 8% to 72%) lower cardiovascular mortality and 53% (29% to 68%) lower all-cause mortality rates in persons with diabetes. For those without diabetes, statin use was associated with a 16% (-24% to 43%) lower cardiovascular and 30% (11% to 46%) lower all-cause mortality rates. Persons with diabetes using statins had a comparable risk of cardiovascular and all-cause mortality as the general population without diabetes. The effect was independent of the level of glycemic control.

Conclusion This observational study lends important support to existing data from randomised clinical trials. Our data suggest that in the general population of older people with diabetes, statin medication markedly reduces the excess cardiovascular and all-cause mortality risk, irrespective of the presence or absence of CHD or glucose-lowering medication.

Article focus

- Clinical trials have shown that statin medication is beneficial for persons with diabetes as regards cardiovascular morbidity and mortality.
- This is not well established except within the rigours of randomised clinical studies.

Key message

- This population-based observational study of older individuals demonstrates that treatment with statins in persons with diabetes reduces cardiovascular mortality rate to a level comparable to what is observed in those without diabetes.
- The effect observed is of comparable magnitude to the effect reported in randomised clinical trials.

Strengths and limitations of this study

- A major strength of the study is the proportionally large national representation in this population-based cohort, the high participation rate and the comprehensive information on morbidity and mortality. The effect observed is of comparable magnitude to the effect reported in randomised clinical trials.
- A limitation is the non-attendance of frail individuals in the study that may cause a possible bias towards more healthy individuals at baseline of this study. Non-attendees in the study have been shown, however, at earlier visits to have comparable levels of conventional cardiovascular risk factors. A limitation is the unavailability of dietary information for this analysis. A weakness in our study is the relatively low number of events during the five-year follow-up. A limitation is the lack of glucose tolerance test for diagnosis of diabetes.

Key words Cohort study, type 2 diabetes, statins, older persons, cardiovascular disease mortality, AGES-Reykjavik

Abbreviations

AGES-Reykjavik, Age, Gene/Environment Susceptibility - Reykjavik Study; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CHD, coronary heart disease; 95% confidence interval, 95%CI; CRP, C-reactive protein; CVD, cardiovascular disease; HbA_{1c}, haemoglobin A_{1c}; ICD-9 and ICD-10, International Statistical Classification of Diseases and Related Health Problems 9^{th} and 10^{th} Revision; MI, myocardial infarction; PCI, percutaneous transluminal coronary intervention; SD, standard deviation; TG, triglycerides; WHO, World Health Organization

INTRODUCTION

The excess risk of vascular disease in persons with diabetes is about twofold compared with those without diabetes and is independent of other conventional cardiovascular risk factors. This was clearly demonstrated in the meta-analysis from 102 prospective trials, recently published by the Emerging Risk Factors Collaboration[1]. The beneficial effects of statins in reducing major vascular events in patients with diabetes, irrespective of their baseline lipid levels, have been demonstrated in a number of randomised clinical trials[2-5]. Additionally, improved life expectancy in recent years of persons with type 2 diabetes, relative to those without diabetes, has been reported[6-8], although a difference still exists. This improvement is possibly a result of better adherence to published clinical guidelines, advocating aggressive multifactorial treatment[9]. However, many patients with type 2 diabetes are still not receiving treatment with statin medication[10, 11]

Although randomised clinical trials have clearly demonstrated the benefit of statin use with regard to cardiovascular morbidity and mortality, every physician will daily face the question whether these trial results apply to his patient. A general population of individuals, with a varied background of co-morbidities which may or may not have excluded them from participation, is not fully represented in the aforementioned trials. This is why it is of key importance to gather confirmatory information from population-based observational studies. One recent prospective population-based study[10] from the U.K. General Practice Database has indeed reported the beneficial effect of statin treatment in lowering all-cause mortality in type 2 diabetes. Older persons are under-represented in clinical trial data and it is therefore particularly important to obtain information on the potential improvement in life expectancy with statin use in older persons with type 2 diabetes, as well as data on the relative impact of lipid lowering treatment in that age group. This will help in clarifying at a population-based level whether current guidelines

should be applied to older persons, who may have had diabetes for an extended period of time.

The present study addresses this information gap by exploring treatment modalities and cardiovascular and total mortality in older individuals with diabetes in the population-based Age, Gene/Environment Susceptibility (AGES)-Reykjavik study.

METHODS

Study population

Between 2002 and 2006 the AGES-Reykjavik study re-examined 5764 unselected survivors of the original cohort who had previously participated in the Reykjavik Study[12]. In the present study 5152 of these survivors are included, with a mean age of 77 years (range 66-96) and a median follow up time of 5.3 years until end of 2009. Informed consent was obtained from all study participants. The Reykjavik Study cohort originally comprised a random sample of 30 795 men and women born in 1907–1935, living in Reykjavik in 1967 that were invited to participate in a long-term prospective cardiovascular survey. A total of 19 381 attended, resulting in 71% recruitment rate [12].

As part of the baseline examination in the AGES-Reykjavik study, a comprehensive questionnaire was administered. In order to eliminate any persons with type 1 diabetes in the study, participants reporting onset of diabetes before the age of 40 were not included; neither were participants not completing their questionnaire or having incomplete data for other study variables included: 66 had missing data about diabetes history on questionnaire; 21 were considered to have diabetes of type 1; 78 had missing data on risk factors (cholesterol, systolic blood pressure, body mass index, triglycerides); 447 had missing HbA1c. Participants were asked to bring all medications and supplements

used in the previous 2 weeks to the clinic. All participants also had a fasting blood specimen drawn and analysed as documented below.

The criteria used for type 2 diabetes diagnosis was either fasting serum glucose of ≥7mmol/l at the visit to the clinic, based on the WHO recommendations from 1999[13], self-reported diabetes in the questionnaire and/or use of diabetes medication.

Blood samples were drawn after overnight fasting. Total cholesterol, HDL cholesterol, triglycerides, high sensitivity CRP, glucose and HbA1c were analysed on a Hitachi 912, using reagents from Roche Diagnostics and following the manufacturer's instructions. LDL was calculated using the Friedewald equation[14].

Blood pressure was measured with a mercury sphygmomanometer with a large cuff, and the mean value of two consecutive blood pressure measurements was used in the analysis. Height and weight were measured and BMI calculated as kg/m^2.

Participants answered questions about frequency of moderate or vigorous physical activity, both current and in midlife. Answers were categorized into never, rarely, occasionally, moderate or high frequency of participation. In this study a binary variable for physical activity was used as an indicator for occasional or higher frequency of participation versus never or rarely participating.

Answers about education were categorized into a binary variable: higher than secondary education versus secondary education or less.

Information on the causes of death was based on data from a complete adjudicated registry of deaths available from the Icelandic National Roster (http://www.statice.is/Statistics/Population/Births-and-deaths). All-cause mortality was defined according to ICD 9-10. In this study we calculated an individual's time at risk from the date of participation in the baseline survey until the date of death from cardiovascular disease (ICD-9 and ICD-10: defined as in the SCORE project[15]) or from all causes, or until the end

of follow-up in the cohort. The information is collected from National Health System Records by the Icelandic Heart Association.

The study was approved by the National Bioethics Committee in Iceland (VSN 00-063) as well as the Institutional Review Board of the Intramural Research Program of the National Institute on Aging and the Data Protection Authority in Iceland.

Statistical analyses

Baseline characteristics of participants by sex and diabetic status in the AGES-Reykjavik study were compared using either linear or logistic regression with age adjustment. Skewed variables were log-transformed. The Cox proportional hazards regression model was used to estimate mortality rates and hazard ratios for the effect of risk factors and statin use. The time on study was used as the time scale. For hazard ratio estimates, an adjustment was made for age and sex in a simple model, and additionally for the following cardiovascular risk factors: cholesterol, HDL-cholesterol, systolic blood pressure, BMI, triglycerides, CRP, hypertensive medication, and current smoking. An additional analysis of mortality rates was done with adjustment for physical activity and education level. A separate term was used in the survival models to represent subgroups, formed by diabetes, history of CHD and statin use. The mortality rate was estimated from the average of the cumulative hazard function after a five-year follow-up and represented as the rate per 1000 person-years. The proportionality assumption for the hazard ratio associated with type 2 diabetes was inspected graphically and by testing the significance of the interaction of type 2 diabetes statuses with the logarithm of the follow-up of time analysed as a time-dependent covariate. Significance testing was two-sided and based on a 5% probability level. We analysed the data using SAS/STAT® software, version 9.2.

RESULTS

The mean age of the 5152 AGES-Reykjavik study participants was 77.0 (±5.8) years, with an age range of 66-96 years. The baseline characteristics in men and women with and without type 2 diabetes according to statin use are shown in Table 1. A higher percentage of individuals with type 2 diabetes were hypertensive than those without diabetes; they also had lower HDL-cholesterol but higher triglycerides and BMI, irrespective of statin use. Statin medication reduced the mean level of total and LDL-cholesterol similarly in those with and without diabetes, or by about 1.2 mmol/l in both men and women. In statin users CRP was lower by 0.30 mg/l in men and 0.50 mg/l in women without diabetes and 0.80 and 1.05 mg/l respectively in those with diabetes. The prevalence of coronary heart disease estimated from hospital records in persons without diabetes using statins, was 71.1% in men and 34.4% in women compared to 7.9% and 2.2% respectively in those not using statins. In individuals with diabetes the coronary heart disease prevalence was 59.4% in men and 24.2% in women using statins, compared to 14.8% and 8.6% respectively in those not on statins. Over 93% of all statin users were hypertensive compared to 78% of non-statin users.

The prevalence of type 2 diabetes and use of glucose lowering treatment in men and women is shown in Table 2. About 16% of men and 9.5% of women in the cohort had type 2 diabetes and the proportion of persons with diabetes undiagnosed at baseline was 31%. In the group with previously diagnosed type 2 diabetes, 23% of the men and 35% of the women controlled their blood sugar level with diet only. As shown in Table 2, less than 7% of persons with diagnosed diabetes were simultaneously taking 3 or 4 drugs for lowering blood glucose. For participants with a prior diagnosis of diabetes, the average time from diagnosis at baseline assessment was just over 10 years.

Effect of statins on cardiovascular and all-cause mortality

The five-year average cardiovascular disease mortality and all-cause mortality rates for those with and without diabetes are shown in Figure 1. Mortality rate is estimated according to statin use and prevalence of coronary heart disease, adjusted to age 75, sex and the mean levels of cardiovascular risk factors (cholesterol, HDL-cholesterol, systolic blood pressure, BMI, triglycerides, hypertensive medication and current smoking) within each cohort. About 26% of men and 16% of women without diabetes and about 35% in both sexes with diabetes were statin users. Statin medication was administered to 69.2% of persons with prevalent coronary heart disease and known diabetes compared to 31.6% of those with known diabetes but without coronary heart disease (Supplement Table 1).

For individuals with diabetes and prevalent coronary heart disease, statin use was associated with a significantly lower rate of cardiovascular disease mortality (Figure 1a) compared to those not using statins, or 11.3 vs. 24.6 per 1000 person years. This amounts to 54% (95% confidence interval 14% to 75%) lower mortality rate in statin users. Similarly statin use was associated with an all-cause mortality rate of 27.8 vs. 63.3 per 1000 person years when comparing the same two groups (Figure 1b), amounting to 55% (31% to 71%) lower mortality rate in statin users. In individuals with diabetes but without coronary heart disease, the rate was 48% (1% to 73%) lower for cardiovascular disease mortality and 52% (26% to 69%) lower for all-cause mortality in the group using statins compared to non-statin users. Combining the groups the hazard of cardiovascular disease mortality was 50% lower in statin users compared to non-statin users and all-cause mortality was 53% lower (Supplement Table 2).

Statin use was associated with 16% (-24% to 43%) lower cardiovascular mortality rate in individuals without diabetes as shown in Figure 1, albeit not statistically significant.

For all-cause mortality statin users had 30% (11% to 46%) lower mortality rate than in non-statin users.

The effect of statins was not modified by the level of HbA1c, the use of oral hypoglycaemic or hypertensive medication, or whether the diabetes was prevalent or newly diagnosed (Supplement Figures 1 and 2).

An additional analysis of mortality rates with adjustment for current physical activity and education level did not have any material effect on the results or the conclusions drawn from the data. The additionally adjusted mortality rates are shown in Supplement Figure 3.

The dramatic effect of statin medication use on mortality rate in persons with diabetes is also reflected in the hazard ratios for the relative risk of cardiovascular and all-cause mortality in individuals with diabetes compared to those without as shown in Table 3. In persons with diabetes and prevalent coronary heart disease not on statins, the relative risk of dying from cardiovascular disease was 3.33 (2.05 to 5.50) when compared to those without diabetes, after adjusting for age, sex and cardiovascular risk factors. The individuals treated with statins, however, had a relative risk of 1.51 (0.83 to 2.75). In persons with diabetes but without coronary heart disease not on statins, the relative risk was 1.40 (1.03 to 1.89) compared to 0.71 (0.31 to 1.62) for those on statins. Adding CRP to the risk factor adjustment showed minimal attenuation of the hazard ratios (Table 3). This implies that the protective effect of statins is not solely attributable to the effect on these cardiovascular risk factors.

DISCUSSION

The major finding in our population-based AGES-Reykjavik study of older individuals with diabetes is the marked improvement in survival associated with statin medication

when compared to those not receiving statins, both with respect to cardiovascular and all-cause mortality. This is independent of prevalent coronary heart disease or glucose-lowering treatment, reducing the mortality rate in individuals with diabetes to a level comparable to those without diabetes.

Statin medication in diabetes has increased gradually during the last decade. Data from the U.K. General Practice Research Database showed an increase in statin use from about 5% in 1996 to 63.5% in women and 71.0% in men in 2005[10], which was associated with hazard ratios of mortality of 0.29 in women and 0.34 in men in the first two years following diagnosis of diabetes. Similarly, in Denmark, only 7% of patients receiving glucose-lowering medication also received statins in 1997, but this had increased to 62% in 2007[11]; information on mortality in that study is however lacking. In our cohort of older persons with diabetes the prevalence of statin medication use was 35% overall. In those with known diabetes but without coronary heart disease the prevalence of statin medication use was 31.6%, but 11.6% in the newly diagnosed without coronary heart disease. One may speculate if this low prevalence of statin use is due to Icelandic physicians' unawareness of results from recent clinical trials or simply their belief that the evidence does not apply to older patients in general.

It is of course well recognised that statin treatment favourably impacts vascular event rates in both those with and without diabetes. In the Heart Protection Study[2] for example it was concluded that 40 mg of simvastatin daily would probably reduce the rate of first major vascular event by about a third. Similarly a two-year treatment period with atorvastatin in type 2 diabetes in the CARDS study reduced the death rate by 27%, prompting an early termination of the trial[16]. The authors concluded that lipid-lowering treatment should at least receive the same attention as glycemic and blood pressure control in type 2 diabetes patients without a history of cardiovascular disease, which is in harmony

with current clinical guidelines. Aggressive multifactorial treatment of high-risk individuals with type 2 diabetes has been shown to be important[9], and may also be appropriate for persons diagnosed above the age of 70. Recent results from several large studies[17, 18] have, however, indicated that caution may be needed as regards aggressive glucose lowering treatment in those with long-established coronary heart disease and diabetes of long duration. In our study, statin use at baseline, but not use of glucose-lowering medication, is associated with the marked reduction of cardiovascular and total mortality rate, reducing mortality in those with diabetes to a level similar to those without diabetes.

Statin medication under the rigors of controlled study conditions in selected individuals has thus been shown to be helpful[2, 4 5]. The novelty of our study is that statin medication also is very likely to be important in older persons in the community, persons which may or may not fit the stringent criteria of normality imposed for inclusion into randomised clinical trials.

Recently a large meta-analysis[1] demonstrated that the increased cardiovascular mortality seen in type 2 diabetes is not explained by conventional cardiovascular risk factors. This suggests that the effect of the statins on cardiovascular mortality seen in our population-based cohort may reach beyond the statins' effect on cholesterol levels, possibly by reducing the damaging effect of inflammatory agents[19, 20]. Inflammation as measured by CRP, however, does not appear to be the explanation in our study, as adjusting for CRP in the risk models did not attenuate the relative risk although those on statins had markedly lower CRP. This warrants further study.

The prevalence of diabetes in Iceland is changing in the same fashion as in other western societies[21]. Furthermore, the Icelandic population is similar to other western populations with respect to cardiovascular morbidity and mortality[22], and our results are

therefore applicable to other Caucasian populations. Thus, considerable additional benefit can be expected by adhering to the current guidelines on statin use in treating individuals with diabetes, also in the older age-groups.

In summary, we have estimated the risk of death from cardiovascular disease and from all causes in a population-based cohort of older persons with type 2 diabetes. The main finding is that statin use, irrespective of glucose-lowering and antihypertensive medication, eliminates the difference in the mortality rate of older persons with type 2 diabetes, compared to those without diabetes. Our study suggests that treatment with statins is paramount in the multifaceted management of type 2 diabetes. Strict adherence to the current guidelines is therefore of key importance for older persons with diabetes, regardless of the presence or absence of cardiovascular disease or the level of glucose or blood pressure control.

Our results urgently call for other population-based studies with comparable information to confirm the effect of statin use on mortality in individuals with type 2 diabetes.

Acknowledgements

This study has been funded by NIH contract N01-AG-1-2100, the NIA Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and Althingi (the Icelandic Parliament). The study is approved by the Icelandic National Bioethics Committee, VSN: 00-063. The researchers are indebted to the participants for their willingness to participate in the study.

Author Contributions: Dr Gudnason had access to all the data and takes full responsibility for the content of this paper. Drafting of the manuscript: Olafsdottir, Aspelund, Benediktsson and Gudnason. Statistical analysis: Olafsdottir and Aspelund. Data collection and preparation: Olafsdottir, Aspelund, Gudnason, Thorsson, Eiriksdottir, Sigurdsson, Launer and Harris. All authors contributed to the interpretation of the results, read and commented on the manuscript and approved the final version.

Conflict of interest statement

Dr Gudnason has funding from National Institutes of Health, Icelandic Heart Association, Icelandic Research Council and the European Union. No conflicts of interest were declared by any other authors.

Funding source's role

The Study's sponsors played no role in the study design, the collection, analysis, and interpretation of data or writing of the report. Dr Gudnason had full access to all the data and had final responsibility for submitting the report for publication.

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Table 1. Baseline characteristics according to statin use in men and women without and with type 2 diabetes (T2D). The AGES-Reykjavik study from 2002-2006.

	Men				Women			
Variables	Statins no		Statins yes		Statins no		Statins yes	
(mean ± SD, IQR or %)	without T2D	with T2D	without T2D	with T2D	without T2D	with T2D	without T2D	with T2D
(number)	(1357)	(230)	(477)	(128)	(2237)	(186)	(442)	(95)
Age in years	77.4 (±5.8)	77.9 (±6.1)	76.0 (±4.8)	75.5 (±4.4)	77.0 (±6.1)	78.7 (±6.0) ***	76.1 (±4.8)	76.3 (±4.5)
Cholesterol mmol/l	5.57 (±0.93)	5.38 (±0.98) **	4.32 (±0.82)	4.14 (±0.84) *	6.19 (±1.05)	5.97 (±1.01) **	4.96 (±0.83)	4.67 (±0.94) **
HDL cholesterol mmol/l	1.46 (±0.40)	1.26 (±0.34) ***	1.40 (±0.37)	1.26 (±0.33) ***	1.75 (±0.45)	1.53 (±0.41) ***	1.70 (±0.40)	1.48 (±0.41) ***
LDL cholesterol mmol/l	3.61 (±0.85)	3.40 (±0.89) **	2.38 (±0.67)	2.21 (±0.68) **	3.90 (±0.98)	3.73 (±0.91) *	2.71 (±0.72)	2.41 (±0.70) ***
TG mmol/l, median (IQR)	0.97 (0.56)	1.33 (0.83) ***	1.01 (0.65)	1.29 (0.98) ***	1.04 (0.63)	1.38 (0.85) ***	1.11 (0.67)	1.57 (0.85) ***
CRP mg/l, median (IQR)	1.90 (2.70)	2.20 (3.53) **	1.60 (2.20)	1.40 (2.10)	2.00 (3.20)	3.15 (5.65) ***	1.50 (2.10)	2.10 (3.30) *
BMI kg/m^2	26.4 (±3.7)	28.3 (±4.2) ***	27.0 (±3.7)	28.4 (±3.7) ***	27.0 (±4.9)	29.0 (±5.5) ***	26.8 (±4.0)	30.2 (±5.1) ***
Systolic BP mm Hg	142.9 (±20.6)	141.1 (±20.7)	144.1 (±20.3)	148.2 (±19.6) ***	142.2 (±21.0)	143.3 3 (±21.8)	143.3 (±20.2)	143.6 (±19.7)
Diastolic BP mm Hg	77.0 (±9.4)	74.7 (±10.8) **	74.4 (±9.7)	74.6 (±10.3)	72.6 (9.3)	70.5 (±10.5)*	71.6 (±10.2)	69.7 (±8.9)
Hypertension %[†]	73.5	88.7 ***	91.6	95.3	78.9	88.7 **	92.5	95.8
Hypertensive medication %	50.0	75.2 ***	85.5	87.5	58.7	79.6***	84.6	90.5
Glucose lowering medication	-	46.1	-	64.1	-	36.6	-	64.2
CHD prevalence %[‡]	7.9	14.8**	71.1	59.4*	2.2	8.6***	34.4	24.2*
Family history MI %	30.1	39.1 **	45.2	41.4	40.2	51.6 **	56.7	53.7
Physical activity in midlife %	51.0	43.9	54.3	45.3	47.1	40.9	50.7	36.8*
Physical activity current %	39.6	27.4***	45.3	35.2*	31.3	26.3	34.2	16.8*
Education, more than secondary%	30.0	27.4	29.8	28.9	21.9	20.4	17.2	16.8
Smoking %	11.9	12.2	9.0	9.4	12.4	10.2	12.9	9.5
Haemoglobin A1c %	5.54 (±0.33)	6.38 (±0.88) ***	5.58 (±0.32)	6.55 (±0.79) ***	5.61 (±0.33)	6.32 (±0.95) ***	5.64 (±0.34)	6.58 (±0.88) ***
Glucose mmol/l	5.57 (±0.50)	7.95 (±2.09) ***	5.58 (±0.53)	7.92 (±2.19) ***	5.44 (±0.51)	7.60 (±2.00) ***	5.41 (±0.52)	7.97 (±2.38) ***

Significance estimates for age-adjusted comparison between those with and without T2D and not using statins (no) and statin users (yes): *p<.05; **p<.01; *** p<.001.
[†]Hypertensive are those with systolic BP>140 mmHg, diastolic BP>90 mmHG or on hypertensive medication.
[‡]Prevalence from history of MI, PCI, and CABG in hospital records.

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Table 2. Prevalence of type 2 diabetes (T2D) and glucose lowering treatment in the AGES-Reykjavik study 2002-2006.

AGES-Reykjavik study	Men	Women	Men and women	% of total T2D
Total T2D at baseline % (n)	16.3 (358)	9.5 (281)	12.4 (639)	100
Diagnosed at study entry % (n)	5.1 (113)	2.8 (84)	3.8 (197)	31
With prevalent T2D at study entry % (n)	11.2 (245)	6.7 (197)	8.6 (442)	69
Mean T2D duration in years (±SD)			10.7 (±10.0)	
Glucose lowering treatment in prevalent T2D				
on special diet only % (n)	23.3 (57)	34.5 (68)		
on diabetic medication % (n)	76.7 (188)	65.5 (129)		
thereof using 1 drug % (n)	*43.7 (107)*	*40.1 (79)*		
" using 2 drugs % (n)	*25.7 (63)*	*19.8 (39)*		
" using 3 drugs % (n)	*6.9 (17)*	*4.6 (9)*		
" using 4 drugs % (n)	*0.4 (1)*	*1.0 (2)*		

Table 3. Hazard ratios (HR) for the relative risk of cardiovascular disease (CVD) mortality and all cause mortality in people with type 2 diabetes (T2D) compared to all non-diabetics according to prevalent coronary heart disease (chd) and statin use*. The AGES-Reykjavik study from 2002-2006.

	Adjusted for age and sex		Adjusted for age, sex, and †CVD risk factors		Adjusted for age, sex, †CVD risk factors and CRP	
	HR	95% CI	HR	95% CI	HR	95% CI
Death from CVD						
All T2D	1.71	(1.35 to 2.17)	1.48	(1.15 to 1.90)	1.45	(1.13 to 1.86)
According to chd and statin use:						
T2D with chd not on statins	4.71	(2.93 to 7.58)	3.33	(2.02 to 5.50)	3.20	(1.94 to 5.29)
T2D with chd on statins	1.92	(1.08 to 3.43)	1.51	(0.83 to 2.75)	1.55	(0.85 to 2.82)
T2D without chd and not on statins	1.53	(1.14 to 2.05)	1.40	(1.03 to 1.89)	1.34	(0.99 to 1.82)
T2D without chd and on statins	0.83	(0.37 to 1.85)	0.71	(0.31 to 1.62)	0.75	(0.33 to 1.69)
Death from all causes						
All T2D	1.44	(1.22 to 1.69)	1.35	(1.14 to 1.61)	1.32	(1.11 to 1.57)
According to chd and statin use:						
T2D with chd not on statins	3.48	(2.43 to 4.99)	2.88	(1.98 to 4.18)	2.72	(1.87 to 3.95)
T2D with chd on statins	1.61	(1.10 to 2.37)	1.34	(0.90 to 1.99)	1.37	(0.92 to 2.04)
T2D without chd not on statins	1.34	(1.09 to 1.64)	1.34	(1.08 to 1.64)	1.27	(1.03 to 1.57)
T2D without chd on statins	0.77	(0.46 to 1.28)	0.70	(0.42 to 1.17)	0.73	(0.44 to 1.23)

*Individuals on statin medication are identified as on statins, those not on statin medication as not on statins.

†CVD risk factors: cholesterol, HDL-cholesterol, systolic blood pressure, BMI, triglycerides, hypertensive medication, and current smoking.

Figure 1. a) Cardiovascular disease (CVD) mortality rate and b) all cause mortality rate per 1000 person years for subjects without type 2 diabetes (not T2D) and with type 2 diabetes (T2D) according to statin use and prevalent coronary heart disease (chd). Rates have been adjusted to age 75, sex and the mean levels of cardiovascular risk factors (cholesterol, HDL-cholesterol, systolic blood pressure, BMI, triglycerides, hypertensive medication and current smoking) within each cohort. Follow up was through 2009 (a median period of 5.3 years) for the AGES-Reykjavik study. The vertical lines represent the mortality rate of all without diabetes (not T2D, N=4513)

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

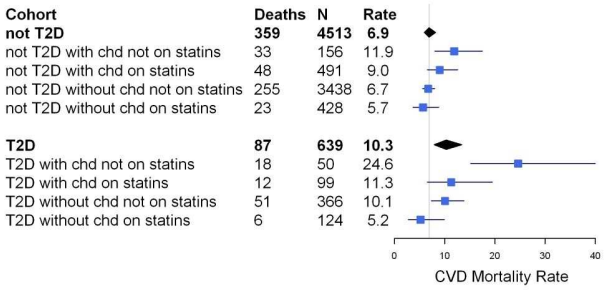
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-7*
Bias	9	Describe any efforts to address potential sources of bias	Not done
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	Separate terms for subgroups in statistical models
		(*c*) Explain how missing data were addressed	6

		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	Not done
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	13
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8-10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Figure 1
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	All analyses are by subgroups
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.



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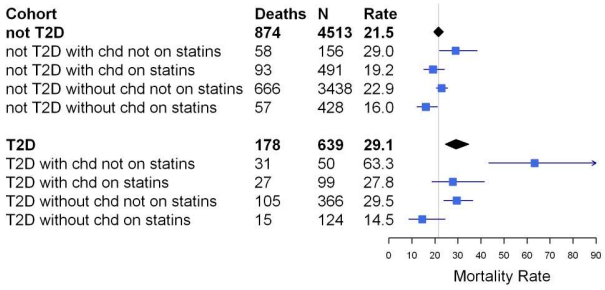

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Effects of statin medication on mortality risk associated with type 2 diabetes in older persons: the population-based AGES-Reykjavik Study

Elin Olafsdottir, Thor Aspelund, Gunnar Sigurdsson, Bolli Thorsson, Gudny Eiriksdottir, Tamara B Harris, Lenore J Launer, Rafn Benediktsson and Vilmundur Gudnason

BMJ Open 2011 1: originally published online June 29, 2011
doi: 10.1136/bmjopen-2011-000132

Notes